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Enhanced Left Ventricular Contractility in Autonomic Failure: Assessment Using Pressure-Volume Relations

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Severe autonomic failure is usually characterized by both supine hypertension and orthostatic hypotension. Inadequate preload reserve, insufficient arterial resistance and abnormal cardiac performance have been postulated to contribute to the hypotension. To clarify these mechanisms, left ventricular performance and contractility were assessed using radionuclide ventriculography and systolic pressure-volume relations when supine and with graded head-up tilt in 11 patients with autonomic failure. Results were compared with those of 12 normal subjects, using phenylephrine infusion for pharmacologic afterload augmentation after autonomic blockade with atropine and propranolol. In a subset of four patients with autonomic failure, systolic pressure-volume relations were similar by both the tilt and phenylephrine methods.

In autonomic failure, end-diastolic volume, end-systolic volume and stroke volume decreased with progressive degrees of tilt ($p \leq 0.007$ for each). The supine radionuclide ejection fraction and cardiac output were similar to those of normal subjects (69% versus 68% and 5.4 versus 4.9 liters/min, respectively, p = NS). However, the slopes of the pressure-volume relations and the supine pressure/volume ratio in autonomic failure were much greater than normal (8.8 versus 2.5, and 6.3 versus 3.6 mm Hg/ml, respectively, $p \leq 0.04$ for both). The baseline total peripheral resistance was greater than normal (24.9 versus 17.4 mm Hg·min^{-1}/liter, p = 0.01), but the resistance at maximal tilt failed to increase (20.8 ± 6.1 units). Plasma norepinephrine concentrations were lower than normal.

Thus, patients with autonomic failure had hypercontractile left ventricular performance when assessed by pressure-volume relations, and their hearts were well matched to the elevated peripheral resistance. There was no evidence that depressed cardiac contractility contributed to orthostatic hypotension in autonomic failure. Rather, a lack of further arterial vasoconstriction and inadequate preload reserve appeared to cause orthostatic hypotension in patients with autonomic failure.

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Autonomic failure is characterized by orthostatic hypotension, postprandial hypotension, impotence and, frequently, supine hypertension (1). It can occur as a primary disorder of the autonomic nervous system or be associated with abnormalities of the central nervous system (2). The pathogenesis of postural hypotension in this disorder is uncertain. Inadequate venous return and insufficient arterial resistance were previously postulated (3) to be the cause, but others (4) have suggested that abnormal myocardial contractility is contributory.

This study was designed to assess left ventricular contractility in patients with autonomic failure by evaluating left ventricular systolic pressure-volume relations. This method is relatively independent of preload and incorporates afterload in its calculation (5). Patients with autonomic failure were uniquely suited for such study because systolic pressure-volume relations could be assessed using supine head-up tilt to alter loading conditions independent of vasoconstricting drugs that might themselves affect left ventricular contractility (6,7).

The results of these studies were compared with those of normal supine subjects after vagal and beta-adrenergic blockade. To assess possible differences in pressure-volume

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relations due to the study design, a subset of patients with autonomic failure was studied with tilt, beta-adrenergic blockade and pharmacologic vasoconstriction while supine.

Methods

Study group. The study was approved by the Institutional Committee for the Protection of Human Subjects. The study group consisted of 23 subjects (12 normal volunteers and 11 patients with autonomic failure). The normal subjects were untrained adults (nine men and three women) whose average age was 32 ± 13 years (range 21 to 69). Each had no known medical disorder, a normal cardiovascular history and a normal physical examination; none was taking any medication. Systolic pressure-volume relations in these subjects have been reported elsewhere (8).

Autonomic failure was confirmed by clinical and biochemical investigations (2). The patients (six men and five women) were generally older than the normal subjects, with an average age of 64 ± 12 years (range 30 to 75). Six patients had peripheral autonomic failure (Bradbury Eggleston syndrome), four had multiple system atrophy (Shy-Drager syndrome) and one had dopamine-beta-hydroxylase deficiency (9). Autonomic failure was confirmed by severe symptomatic postural hypotension, supine hypertension, subnormal norepinephrine response to upright posture and abnormal cardiovascular responses to the Valsalva maneuver, handgrip and cold pressor testing (2,10). Each had a normal cardiac examination, except for one patient who had a systolic nonejection click but no mitral regurgitation. The electrocardiograms were either normal or had minor nonspecific ST-T abnormalities; none displayed left ventricular hypertrophy.

Normal subject protocol. Normal subjects were studied supine in the fasting state. Intravenous cannulas were inserted into right and left forearm veins for blood sampling and drug infusions. Atropine and propranolol were infused for vagal and beta-adrenergic blockade. A radionuclide ventriculogram was recorded to estimate left ventricular volume, and the auscultatory blood pressure was measured simultaneously at 1 min intervals during the ventriculogram. Systolic blood pressure was then increased by intravenous infusion of phenylephrine. Two additional data points were obtained in a similar manner when systolic blood pressure was stable and had increased by approximately 15 and 30 mm Hg above the baseline value.

Autonomic failure protocol. The patients were studied when fasting and supine for 12 h. All medications were discontinued at least 3 days before the study. Radionuclide and blood pressure data were collected when supine and with preload reduction utilizing an electric tilt table. The degree of tilt was designed to reduce systolic blood pressure in stages by approximately 15% and then 30% of the supine value.

Although all of the patients had severe autonomic failure, cardiac denervation might have been incomplete. Also, there might have been effects on the pressure-volume relations produced by preload reduction rather than afterload augmentation. Thus, a subgroup of four patients with autonomic failure underwent further study to determine the effects of beta-adrenergic blockade and pharmacologic afterload augmentation on pressure-volume relations. Blood pressure and radionuclide ventriculograms were obtained with these patients supine and with two stages of tilt, as already described. Propranolol was then infused according to the same protocol utilized in normal subjects, and head-up tilt was repeated with similar data acquisition. Finally, the patients were returned to the supine position, and blood pressure was allowed to stabilize. Systolic blood pressure was then increased with phenylephrine as before, and two further images were obtained when systolic pressure had increased by approximately 15 and 30 mm Hg above the baseline value. In preliminary studies, an additional three normal subjects were studied with supine tilt after beta-adrenergic blockade. Their changes in blood pressure were slight, and it was judged more useful to perform the additional studies on the patients with autonomic failure to examine the effects of our methods for altering left ventricular loading conditions.

Radionuclide imaging. Red blood cells were labeled in vivo by injection of 1.5 mg of stannous pyrophosphate, followed in 20 min by 25 mCi of technetium-99m pertechnetate (11). Gated equilibrium images of the cardiac blood pool were collected in the left anterior oblique projection with a PhoGamma IV scintillation camera (Siemens) using a low energy all-purpose collimator and a symmetric 20% window. The camera was interfaced to a PDP 11/40 computer (Digital Equipment), and images were collected using a 64 × 64 image matrix, 30 ms/frame, 20 frames/cardiac cycle and variable zoom hardware for magnification of the heart. Images were collected for at least 2 million counts (usual duration 5 min). At the end of each collection, a 5 ml blood sample was drawn through an intravenous cannula in the right arm into a heparinized syringe to serve as a calibration standard for subsequent left ventricular volume estimation. Each sample was transferred into a Petri dish, using a pipette with a 0.5% error full scale (Oxford Macro-Set, Sherwood Medical). Samples were placed on the collimator and counted for 5 min at the end of the study.

Blood pressure measurements. Blood pressure was estimated every minute during imaging using an aneroid cuff sphygmomanometer applied to the right arm, with auscultation of phases 1 and 5 of the Korotkov sounds.

Drug infusion. Vagal (normal subjects only) and beta-adrenergic blockade was achieved with atropine and propranolol, respectively. Atropine (0.2 mg/ml) was infused over 10 to 15 min to a total loading dose of 0.04 mg/kg, and then a maintenance infusion was begun at 1.1 μg/kg per min. Propranolol was infused simultaneously in normal subjects

and in the subset of four patients with autonomic failure to a total dose of 0.2 mg/kg. The maintenance dose was 1.1 μg/kg per min.

Phenylephrine was infused in all normal subjects and in the four patients with autonomic failure who underwent beta-adrenergic blockade. Phenylephrine was infused into the left forearm cannula at an initial rate of 0.2 μg/kg per min, and the rate was increased progressively to achieve increments in systolic blood pressure.

Data Analysis

Estimation of systolic pressure-volume relations depends on the accurate determination of blood pressure and the accuracy of estimating end-systolic volume and small *changes* in end-systolic volume.

Blood pressure. The five to six estimates obtained during each radionuclide ventriculogram were averaged to obtain the average systolic pressure during an average cardiac cycle. In nine consecutive catheterized patients, we found a close correlation between systolic cuff blood pressure (mm Hg) and systolic pressure in the ascending aorta (cuff = $-1.68 + 1.03 \times$ aortic; $r = 0.991$, $p < 0.001$).

Radionuclide ventriculograms. Each study was analyzed in duplicate for left ventricular end-diastolic volume, end-systolic volume, ejection fraction and cardiac output. We previously demonstrated a strong correlation between radionuclide and contrast methods for estimating left ventricular ejection fraction ($r = 0.93$) (12) and left ventricular volume (8) by the method of Dehmer et al. (13), with <2% intraobserver error (8). We have also demonstrated (14) that the mean correlation (r) for estimating *changes* in end-systolic volume was 0.90 in dogs, comparing near simultaneous contrast and radionuclide studies. Such volume changes averaged only 11.9 ml (range 0.3 to 38.1).

The total peripheral vascular resistance was calculated as the ratio of mean arterial pressure divided by the radionuclide angiographic cardiac output and expressed in "units" with the dimensions of mm Hg·min^{-1}/liter.

Pressure-volume relations. Systolic pressure-volume relations were evaluated by two methods. The relation of peak systolic pressure to end-systolic (end-ejection) volume (*pressure-volume relation*) was assessed during tilt, before and after autonomic blockade and during phenylephrine infusion, as applicable. For this, the pressure and volume data were graphed for each individual. By linear regression analysis, the slope and the extrapolated value of the end-systolic volume at a systolic pressure of zero (V_0) were calculated. Also, during each stage of the protocol, the ratio of peak-systolic pressure to left ventricular end-systolic volume was calculated (*pressure/volume ratio*).

Statistical analysis. All data were entered into a medical data base system (CLINFO, supplied to Vanderbilt University by the Division of Research Resources, National Institutes of Health, Bethesda, Maryland). Repeated measures were analyzed by one-way analysis of variance and, when significant differences were detected, by the Student-Newman-Keuls test. Unpaired *t* tests were used to compare the results from the autonomic failure and normal groups. Linear regression analysis was used to determine the slopes of the pressure-volume relations. The data from patients with autonomic failure and normal subjects were compared at baseline conditions. Also, the pressure-volume relations of patients with autonomic failure were compared with those of normal subjects after the administration of atropine and propranolol. Group results were expressed as mean values ± SD. In each comparison, the null hypothesis stipulated that the results were not different. If differences were detected, statistical significance was ascribed at a p value <0.05.

Results

General results. The study protocol was well tolerated in normal subjects and those with autonomic failure. There was no chest pain or electrocardiographic evidence of myocardial ischemia; side effects were rare. Orthostatic hypotension after "autonomic blockade" occurred in some normal subjects. This was adequately treated by infusion of 1 liter of normal saline solution after the study. Restlessness sometimes occurred, but resolved a few minutes after stopping the drug infusion. Clinical features, blood pressure response to tilt and the cold pressor test results of patients with autonomic failure are shown in Table 1.

Baseline supine systolic blood pressure was significantly higher in the patients with autonomic failure compared with normal subjects (176 ± 22 versus 111 ± 6 mm Hg, $p < 0.001$), and the heart rate was also higher (75 ± 13 versus 63 ± 10 beats/min, $p = 0.02$). However, left ventricular end-diastolic volume (107 ± 33 versus 118 ± 35 ml), end-systolic volume (35 ± 19 versus 39 ± 15 ml), stroke volume (72 ± 17 versus 79 ± 23 ml) and cardiac output (5.4 ± 0.4 versus 4.9 ± 1.4 liters/min) were similar in the patients with autonomic failure and normal subjects, respectively. Total peripheral vascular resistance was much greater in the patients with autonomic failure than in normal subjects (24.9 ± 7.7 versus 17.4 ± 5.5 units, $p = 0.01$).

With maximal head-up tilt, stroke volume in the patients with autonomic failure decreased to 54 ± 22 ml and cardiac output decreased to 4.3 ± 1.8 liters/min ($p = 0.007$ for both). However, total resistance did not change significantly (20.8 ± 6.1 units, $p = 0.45$).

Pressure-volume relations. Systolic blood pressure decreased from 176 ± 22 to 137 ± 23 mm Hg (22%) during the initial degree of tilt ($p < 0.001$) and then to 103 ± 20 mm Hg (41%) with the greater degree of tilt ($p < 0.001$). Left ventricular end-diastolic volume decreased sharply from 107 ± 33 to 78 ± 32 ml at the greater degree of tilt ($p <$

Table 1. Clinical Features of 11 Patients With Autonomic Failure

Patient No.	Age (yr)/ Gender	Dx	Supine			Tilt			Cold Pressor	
			BP	HR	NE	BP	HR	NE	Δ MAP	Δ HR
4	64/M	MSA	170/120	100*	211	80/50	100*	232	5	0*
1	67/F	MSA	180/100	74	96	80/60	80	112	0	2
2	64/F	MSA	150/100	80	233	90/60	82	295	13	7
3	77/M	IOH	210/110	45	37	60/40	45	28	0	0
6	80/M	IOH	160/98	88	44	50/30	100	67	5	0
7	70/F	IOH	170/90	76	156	112/70	88	169	10	3
8	64/M	IOH	177/98	77	56	123/82	79	80	7	16
9	65/M	IOH	175/108	61	199	94/72	77	252	8	10
10	62/M	IOH	146/98	79	56	92/72	74	80	7	4
11	59/F	IOH	170/100	76	30	60/46	84	30	0	−2
5	34/F	DBH	130/70	74	<5	60/40	84	<5	0	8
Mean	64		167/99	76	102	82/57	81	123	5	5
SD	12		21/13	14	82	23/17	15	99	5	5
SE	4		6/4	4	25	7/5	5	30	2	2

*Ventricular demand pacemaker. BP = blood pressure (mm Hg); DBH = dopamine β-hydroxylase deficiency; Dx = diagnosis; F = female; HR = heart rate (beats/min); IOH = idiopathic orthostatic hypotension; M = male; MAP = mean arterial pressure; MSA = multiple system atrophy; NE = norepinephrine (pg/ml); Δ = change.

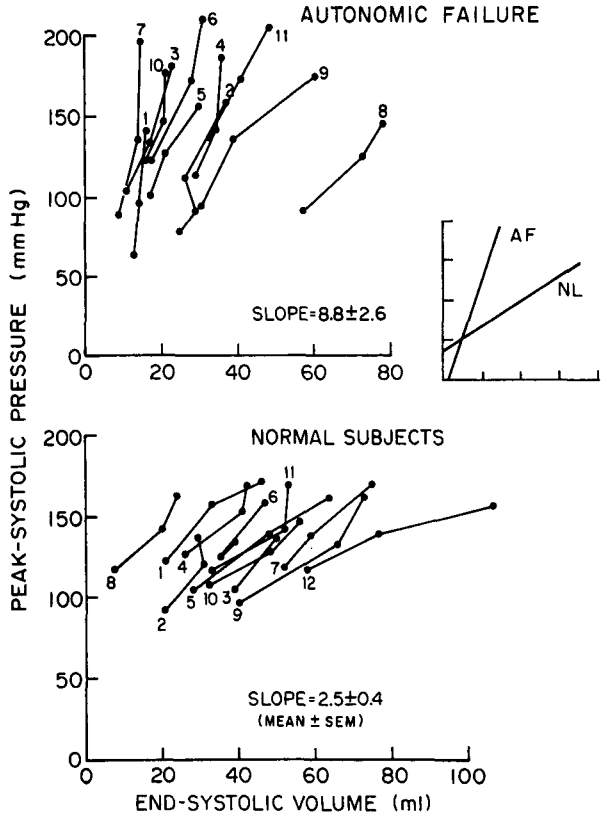
0.001), and end-systolic volume decreased from 35 ± 19 to 24 ± 13 ml ($p < 0.001$).

With phenylephrine, in the normal subjects, systolic pressure increased from 113 ± 12 mm Hg to a peak value of 159 ± 12 mm Hg (41% increase, $p < 0.001$). In the subset of four patients with autonomic failure who underwent further study, the supine systolic blood pressure was 151 ± 35 mm Hg after the initial stages of tilt and propranolol. With phenylephrine, systolic pressure increased to 204 ± 23 mm Hg (38% increase, $p < 0.02$). During phenylephrine infusion, heart rate changed only slightly, increasing by an average of 5 beats/min in normal subjects and 4 beats/min in the patients with autonomic failure.

Systolic pressure-volume relations are illustrated in Figure 1. The average slope of these relations was significantly greater in those with autonomic failure than in normal subjects (8.8 ± 8.7 versus 2.5 ± 1.5 mm Hg/ml, $p = 0.02$), suggesting that left ventricular contractility was increased in patients with autonomic failure. The estimated ventricular volume at zero pressure (V_0) was greater in the patients with autonomic failure than in normal subjects (2 ± 10 versus −28 ± 32 ml, $p = 0.007$), as was the supine pressure/volume ratio (6.3 ± 3.1 versus 3.6 ± 2.8 mm Hg/ml, $p = 0.04$) (Fig. 2), in contrast to the ejection fraction, which was not significantly different from that in normal subjects.

Effects of autonomic blockade and afterload on pressure-volume relations. Figure 3 displays the pressure-volume relations in the subset of four patients with autonomic failure who underwent further study to investigate possible methodologic differences. Before blockade, the data were linear; by linear regression analysis, r values ranged from 0.87 to 0.999 (Fig. 3, curve A, each panel). After propranolol, there was slight left ventricular dilation. During phenylephrine infusion, the results showed similar linearity; by linear regression analysis, r values ranged from 0.95 to 0.99 in three patients, each of whom had three data points for this curve (curve C). In contrast, during tilt after infusion of propran-

Figure 1. Systolic pressure-volume relations in patients with autonomic failure (AF) compared with normal subjects (NL). Data were linear, and the slopes in patients with autonomic failure were much greater than normal.



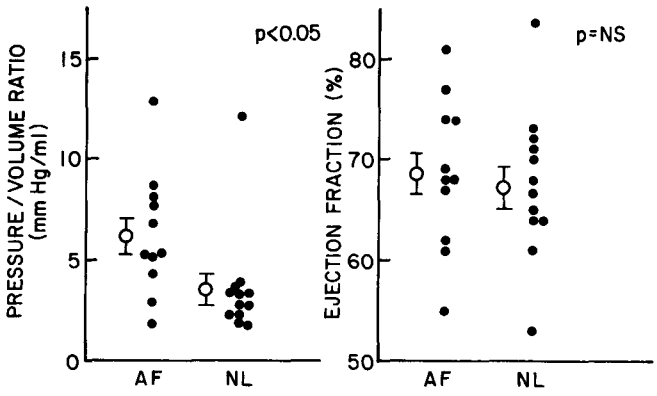


Figure 2. Systolic pressure/volume ratio and ejection fraction in 11 patients with autonomic failure (AF) and 12 normal subjects (NL). The left ventricular pressure/volume ratio was higher in those with autonomic failure, and there was little overlap with the normal group. In contrast, ejection fraction was similar in both groups.

olol, two of the patients had sudden marked left ventricular dilation as the systolic pressure decreased to its minimum (curve B). The slope of the pressure-volume relations in these two patients was calculated by excluding the sharp deviations in curve B (Table 2). After these exclusions, there was no significant difference among curves A, B and C by analysis of variance ($F = 1.03$, $p = 0.39$). Therefore, it was unlikely that the increased slope with tilt in the group of 11

Figure 3. Effects of loading conditions and beta-adrenergic blockade on pressure-volume relations in four patients with autonomic failure. There was no systematic difference between the results using head-up tilt (**curve A**), head-up tilt after propranolol (**curve B**) and supine phenylephrine infusion after propranolol (**curve C**) once points showing sudden ventricular dilation at lowest systolic pressure were excluded (**curve B, top two panels**). See text for details.

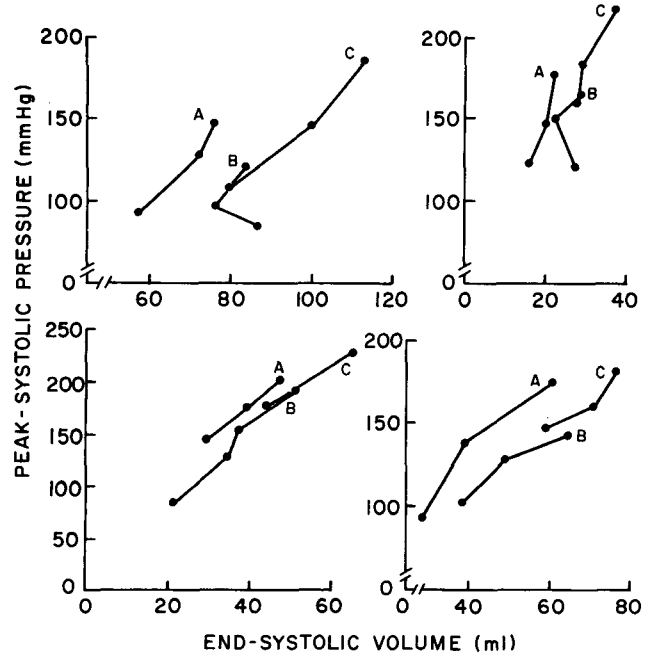


Table 2. Slopes of Systolic Pressure-Volume Relations in the Subset of Four Patients With Autonomic Failure

Patient No.	Curve A (tilt)	Curve B (tilt + propranolol)	Curve C (supine + propranolol + phenylephrine)
8	6.5	0.9	5.3
9	2.5	1.5	1.9
10	2.5	3.0	2.4
11	3.8	3.6	3.5
Mean	3.8	2.3	3.3
SD	1.9	1.3	1.5
SE	0.9	0.7	0.8

patients with autonomic failure was due to different methods of altering ventricular pressure and volume.

Plasma catecholamines. The results of plasma norepinephrine and epinephrine determinations are shown in Figure 4. The supine norepinephrine levels were low compared with normal levels established in this laboratory (15) when the age of the patients was taken into account. With the exception of one patient, there was only minimal increase in norepinephrine during tilt. Epinephrine tended to increase with tilt, but the change was not statistically significant. There was no correlation between the slope of the pressure-volume relations and the plasma epinephrine or norepinephrine concentration when the patient was supine or at maximal tilt.

Discussion

Patients with autonomic failure were studied with radionuclide ventriculography to assess left ventricular performance. Contractility was estimated by systolic pressure-volume relations. There is little information about whether abnormal left ventricular contractility contributes to the orthostatic hypotension in this disorder. Autonomic failure also offered a special opportunity for the study of left ventricular contractility because these data could be obtained by systematic tilt-induced alterations in pressure and volume, rather than by pharmacologic methods.

Characteristics of autonomic failure. These 11 patients had numerous classic features of autonomic failure, including supine hypertension (16), severe orthostatic hypotension (2), inadequate response of mean arterial pressure or heart rate to the cold pressor stimulus (17), low circulating norepinephrine levels (18) both supine and with head-up tilt and low renin levels (19). Adrenomedullary function is better preserved than is sympathetic neural function in this disorder (2).

Hemodynamics. Systemic arterial blood pressure and cardiac output declined with progressive degrees of head-up tilt in these patients with autonomic failure. Because heart rate remained relatively constant, the mechanisms that might have reduced cardiac output were inadequate preload,

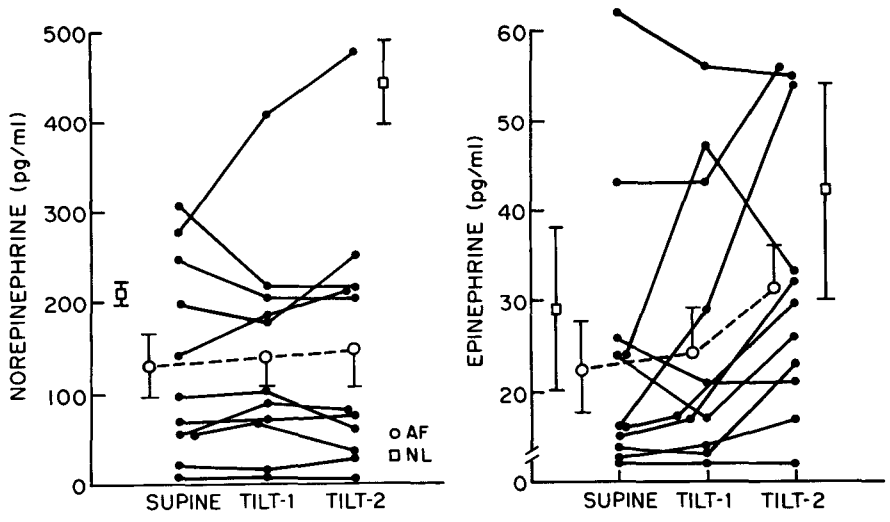


Figure 4. Plasma norepinephrine and epinephrine with two progressive states of head-up tilt in the autonomic failure (AF) group. There was wide variability among patients. Neither norepinephrine nor epinephrine increased significantly. Normal (NL) values are shown for comparison.

excessive afterload and depressed cardiac contractility. When supine, left ventricular end-diastolic and end-systolic volume, ejection fraction and cardiac output determined by radionuclide ventriculography were similar in patients with autonomic failure and normal subjects, even though systemic arterial blood pressure and total peripheral resistance in the former were much greater than normal. With tilt, there was a profound decrease in end-diastolic volume, end-systolic volume and cardiac output.

There is usually a compensatory increase in arterial resistance that maintains blood pressure in the normal range (3,4), but resistance did not increase in these patients. Hickam and Pryor (3) concluded that inadequate arteriolar vasoconstriction, coupled to a deficiency in venous tone, was responsible for the postural hypotension in patients with idiopathic or neurologically associated orthostatic hypotension. Our results confirmed this. Ibrahim et al. (4) found that supine cardiac output, total blood volume and indirect estimates of cardiac contractility were reduced in autonomic failure; however, our present results did not confirm their output or contractility data.

Venous return is an important regulator of cardiac output because 60% to 80% of blood volume resides in these capacitance vessels. Steady-state changes with passive upright tilt in humans include a 20% to 30% decrease in cardiac output (4,20,21) and pooling of approximately 7 ml/kg of blood in the lower limbs (22). Patients with orthostatic hypotension and normal subjects both pool similar amounts of blood in the legs during head-up tilt (23). Carotid sinus hypotension in an anesthetized canine preparation can cause rapid reflex venoconstriction (24), but head-up tilt in normal subjects causes only transient venoconstriction despite venous pooling (25,26). Possibly, the lack of profound systemic hypotension prevents sustained venoconstriction in normal subjects, whereas the lack of efferent sympathetic function prevents this compensation in those with autonomic failure. The slight decrease in blood volume detected by Ibrahim et al. (4) might also contribute to postural hypotension in autonomic failure.

Indexes of contractility. Ventricular contractility was assessed using systolic pressure-volume relations (4). End-systolic elastance (E_{es}) is an index of contractility that is relatively independent of end-diastolic volume (27), influenced only moderately by heart rate (28), approximately linear in the normal operating range (29,30) and described by the equation $E_{es} = P_{es}/(V_{es}-V_0)$, where P_{es} is the ventricular pressure at end-systole, V_{es} is the end-systolic volume and V_0 is the volume at 0 pressure (5). In this system, end-systole is defined as the time (t) of peak elastance when solving the equation $E(t) = P(t)/[V(t) - V_0]$. In this study, peak systolic pressure was substituted for P_{es}, and end-ejection volume was substituted for end-systolic volume. This allowed more convenient estimation of the systolic pressure-volume relation. Others (31–33) have shown that using peak systolic pressure and end-ejection volume affords similar estimates of left ventricular contractility, although the values for pressure-volume relations are slightly greater when using these rather than end-systolic values.

The pressure/volume ratio (P_{es}/V_{es}) is a reasonable approximation of end-systolic elastance (E_{es}) if the volume at 0 pressure (V_0) is close to 0 or if V_{es} is much greater than V_0. However, the numeric value of the pressure-volume ratio is not equal to E_{es}, because the term V_0 is neglected. The values for E_{es} and pressure/volume ratio correlate well (31), and both change with the contractile state (8,34).

The pressure-volume relations after autonomic blockade simulated the condition of patients with autonomic failure and are more reproducible than before blockade (35). Thus, we employed these data in normal subjects for comparison with patients with autonomic failure.

Systolic pressure-volume relations in these patients were assessed by passive head-up tilt, which reduced preload, rather than by infusing a pharmacologic vasoconstrictor to increase pressure afterload. This was advantageous because

it avoided the potential confounding effects of vasoconstricting drugs on the myocardium (6,7,36,37). The above normal supine pressure/volume ratio and the increased pressure-volume relations in those with autonomic failure compared with normal subjects were mutually consistent. Both implied enhanced contractility despite greater total peripheral resistance than normal.

Possible Mechanisms for Hypercontractility

Effect of hypertrophy. Hypertension can cause hypertrophy and hypercontractility as judged by pressure-volume relations (38,39). Supine hypertension might have produced hypertrophy. However, the electrocardiograms (ECGs) showed no hypertrophy, and echocardiograms in each of four patients were normal, excluding this mechanism.

Curve shifts: effects of loading conditions or ischemia. Independent of slight curvilinearity of the normal pressure-volume relation (29,30), several conditions might have produced inapparent shifts from one pressure-volume curve to another, causing artifactually steeper pressure-volume relations. Ventricular interaction (40), shortening deactivation (27) or ischemia (41) might cause such shifts in this setting. First, head-up tilt could have decreased left ventricular pressure by reducing ventricular interaction (40). Second, tilt might have favored left ventricular ejection by reducing afterload. This would further enhance the phenomenon termed "shortening deactivation" (27), and with lowered systolic pressure, produce apparently steeper pressure-volume relations. Third, ischemia, induced by hypotension is known to cause progressive curve shifts (41).

However, it is unlikely that "curve shifts" are responsible for our results. First, the supine pressure/volume ratio was greater in patients with autonomic failure than in normal subjects, supporting the concept that the ventricle was hypercontractile at baseline study. Second, slopes of the pressure-volume relations were similar, whether by tilt before propranolol infusion (curve A) or when supine during phenylephrine infusion (curve C) (Fig. 3). Recently, Kass and Maughan (42) anecdotally reported no difference in systolic pressure-volume relations in patients studied with vena cava occlusion compared with isometric hand-grip (their Fig. 6), confirming our conclusion that phenylephrine and tilt produced similar results. Third, ischemia was unlikely because no patient had ECG changes or regional wall motion abnormalities with tilt. However, at the extremes of tilt after infusion of propranolol (Fig. 3, curve B), there was a sharp increase in left ventricular volume in two patients; this exceptional dilation might have been caused by ischemia. This is similar to findings in the isolated heart (41) and may confirm the concept in patients. We believe that the differences in contractility between patients with autonomic failure and that in normal subjects were not due to our methods of altering loading conditions.

Denervation hypersensitivity. In denervated reserpinized cat papillary muscles, contractility is normal despite norepinephrine depletion (43). There is a supernormal response to exogenous norepinephrine (43). In autonomic failure, there is marked hypersensitivity to the effects of isoproterenol (44), based on heart rate and blood pressure responses. Furthermore, in ancillary studies, we have documented a significant denervation hypersensitivity of cardiac output in patients with autonomic failure in response to isoproterenol. With administration of propranolol at 1.1 mg/min for 10 min, followed by 0.05 mg/min thereafter, we consistently observed a 40-fold shift in the dose-response curve for isoproterenol in terms of cardiac output. Although our results do not conclusively exclude that denervation hypersensitivity might be a potential mechanism for the increase in contractility, this seems unlikely because the slopes of the pressure-volume relations did not decrease after propranolol doses that were even higher than those previously employed. In addition, there was no correlation between the plasma catecholamines and systolic contractile indexes.

Intracellular metabolism. The increased contractility and increased peripheral arteriolar tone could be due to abnormal calcium, sodium or potassium handling. In particular, abnormal calcium metabolism has recently been postulated (45) in two low renin states: 1) low renin essential hypertension, and 2) primary aldosteronism with lower serum-ionized calcium and increased intracellular accumulation of calcium; the latter can increase arteriolar resistance. Plasma renin activity levels are almost undetectable in autonomic failure (46). This is assumed to be a result of inadequate sympathetic stimulation of renin release. It is possible that suppression of plasma renin activity by this mechanism may duplicate the abnormal intracellular calcium accumulation found in the two pathologic processes just mentioned. In this case, a generalized excess of intracellular free calcium would enhance contractility and increase vascular resistance as well.

Cardiac-arterial coupling. Supine stroke volume was normal in the group with autonomic failure. The enhanced left ventricular contractility could simply be an obligatory adaptive response for effective pumping into a constricted arterial system (47). Apparently, there was no such adaptation by the venous capacitance system, because end-diastolic volume decreased sharply with upright tilt.

Conclusions. The circulatory responses to supine head-up tilt were characterized in patients with autonomic failure using radionuclide ventriculography and systolic pressure-volume relations. It was demonstrated that there was inadequate arteriolar constriction and venous return in response to head-up tilt. Left ventricular contractility was enhanced—not depressed—in this disorder and did not contribute to the hypotension.

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